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On Colorectal Polyps and Carcinoma
with Special Reference to
their Interrelationship

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Malmö 1974

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The present dissertation is based on the following papers:

- I. Ekelund, G. 1963. On cancer and polyps of colon and rectum. Acta Pathol Microbiol Scand 59, 165-170.
- II. Berge, T., Ekelund, G., Mellner, C., Pihl, B. & Wenckert, A. 1973. Carcinoma of the colon and rectum in a defined population. An epidemiological, clinical and postmortem investigation of colorectal carcinoma and coexisting benign polyps in Malmö, Sweden. Acta Chir Scand, Suppl. 438.
- III. Ekelund, G. & Pihl, B. 1974. Multiple carcinomas of the colon and rectum. Cancer. In press.
- IV. Ekelund, G. & Lindström, C. 1974. Histopathological analysis of benign polyps in patients with carcinoma of the colon and rectum. Submitted for publication in Gut.
- V. Brahme, F., Ekelund, G.R., Nordén, J.G. & Wenckert, A. 1974. Metachronous colorectal polyps. A comparison between the development of colorectal polyps and carcinomas in persons with and without polyps in their history. Dis Colon Rectum. In press.

The publications are referred to by their Roman numerals in the text.

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INTRODUCTION AND PURPOSE

Colorectal adenocarcinoma is, besides adenocarcinoma of the breast, the most common type of malignant tumour in Sweden (Cancer Incidence in Sweden, 1970). Broadly speaking, the prognosis now seems to be rather stable. In most series, survival is directly related to the stage of the tumour according to Dukes (1932), and it has been emphasized (Bacon, 1971; Sanfelippo & Beahrs, 1972) that the prognosis would be better if lesions could be detected and removed while still in an early stage. This was realized by Hultborn, who in 1952 stated that "cancer of the colon and the rectum is no longer in the main a therapeutic problem, but a diagnostic one". During the two decades following this statement new diagnostic methods, such as double contrast technique for radiographic examination of the colon-rectum and colonoscopy have made it possible to detect even tiny mucosal lesions. When such lesions can be recognized as malignant, surgery is clearly indicated, but otherwise the choice of treatment depends on their relationship to carcinoma.

Many investigators have been concerned with the significance of benign colorectal polyps, particularly adenomas, as precursors of carcinoma. It is here not intended to review the extensive literature completely, reference will instead be made to reviews and monographs (Turell & Haller, 1964; Welch, 1964; Burns, 1966; Castleman & Krickstein, 1966; Hultborn,

1968; Jackman & Beahrs, 1968; Andreassen, 1969; Morson & Bussey, 1970; Buntain, ReMine & Farrow, 1972).

No unanimity has been achieved on the relationship between adenoma and carcinoma. Many authors state that there is a clear relationship and that carcinoma often originates in a benign polyp, while others postulate that carcinoma arises directly from the mucous membrane. This lack of unanimity can probably be explained, at least in part, by the fact that much of our present knowledge is based on circumstantial or indirect evidence (Turell & Haller, 1964). Much of the confusion can probably be attributed to differences in nomenclature and use of imprecise designations as well as to differences in composition of materials and populations and examination methods (Chapman, 1963; Turell & Haller, 1964; Morson & Bussey, 1970).

An ideal material for the study of the relationship between polyps and carcinoma would be a complete series from a defined population. Such a material is difficult to collect, but, as shown by other investigators (e.g. Berge, 1967; Bjerre, 1969; Langeland, 1970), the town of Malmö lends itself especially well to epidemiological studies, because it has a well defined population, and as far as the medical service is concerned, it is a separate region. This was considered to justify the present investigations which were partly stimulated by the keen interest long taken in colorectal polyps at Malmö General Hospital (Andrén, Frieberg & Welin, 1955; Winblad & Frieberg, 1956; Wenckert, 1963; Welin, 1967).

The purpose of the present investigation of the colon-rectum, was to appraise, in a defined population:

- a) the incidence of carcinoma;
- b) the frequency of cases with carcinoma at necropsy;
- c) the frequency of cases with benign polyps at necropsy and at time of operation for coexisting carcinoma;
- d) the sub-site distribution of benign polyps and carcinoma;
- e) the frequency of various histological types of benign polyps;
- f) the risk of appearance of new, benign or malignant, tumours in patients with polyps.

The relationship between benign polyps and carcinoma was assessed on the basis of these findings.

Three separate materials were used, one necropsy, one clinical and one radiographic series. Items a and e above were studied in the clinical series, b, c and d in the clinical as well as in the necropsy series and f in the radiographic series.

II

GENERAL MATERIAL AND METHODS

Material and methods common to all parts of the investigation are described here, while material and methods specific for the various parts of the investigation are described in association with the results of each part.

Characteristics of the population and medical service in Malmö

- a) The population is well defined. During 1958-1967 the average number of inhabitants in the town of Malmö was 238,797. Annual figures for age- and sex-distribution are available. The population above 25 years comprised about 3 % more females than males.
- b) The population is rather stable. In the years 1963-1967, on the average, 4.3 % moved into the town and 3.8 % moved out.
- c) Only one hospital is available for the inhabitants. With very few exceptions all patients with colorectal carcinoma diagnosed intra vitam are taken care of at the only surgical department.
- d) The rate of necropsy is high. About 99 % of all the patients who died in the hospital during the time of the present investigation were necropsied. The necropsy rate for the entire population of the town increased from 58.6 % in 1958 to 86.4 % in 1967 (II).

Collection of data

A special registry and follow-up unit for patients with colorectal carcinoma was set up at the Department of Surgery in 1958. Data relevant to the present investigation were collected from patients records, which included necropsy protocols and reports of histopathological examination of surgical specimens (I), reports of radiographic findings and of examinations at the out-patient-unit as well as the main records from the Department of Surgery (II, III, IV). In part of the material all available histological specimens were reviewed (IV, V), and in part of the material all radiographs were re-examined.

Handling of data

Data were handled either with the aid of punch cards (Sorto) (I), combination punch cards (KH-Systemer, Denmark) (IV) or with a computer (Datasaab D 21, System J 5) (II, III). Analyses of probability were performed with standard statistical methods. Results of these statistical analyses are summarized in the appendix.

General principles of the examinations

The examination methods and diagnostic criteria were those used routinely at Malmö General Hospital.

Pathologic-anatomical examinations. The entire large intestine was always slit up at necropsy, and surgical and necropsy specimens were rinsed and inspected with the naked eye. Lesions found were as a rule examined histologically.

Radiographical examinations. The double contrast method was generally used except in emergency cases. Even in patients with rectal carcinoma the entire large bowel was, as a rule, examined preoperatively with the double contrast method. When the diagnosis was based on radiography alone, only polyps demonstrated radiographically on at least two occasions were accepted as such.

Clinical examinations. The preoperative examination of patients with suspect, or already diagnosed, colorectal tumours included rectoscopy. Surgical specimens were after gross inspection referred for pathological examination.

COMMENTS

Since a large part of the data were collected in retrospect, essential information was sometimes difficult to evaluate and even missing, and then mainly on the size and site of polyps as well as on histologic analysis. In the clinical series (II, III, IV), which were partly prospective, this source of error was somewhat smaller, since it was possible to compare different reports on the same item, such as reports from radiographic, rectoscopic, surgical and pathologic-anatomical examinations.

Most classifications used have arbitrary borderlines which are by no means distinct, e.g. borderlines between segments of the large bowel, between different morphological types of adenomatous lesions and between groups with histologically different grades

of epithelial atypia. It should also be recalled that only clinical routine methods were used. These factors must be kept in mind when the results are evaluated but the present investigations reflect fairly well what findings might be expected at routine clinical, and clinical-pathological examinations.

DEFINITIONS

Polyp

A broad clinical term, used to describe any mass of tissue, projecting from the surface of the colorectal mucosa, In histopathological descriptions by polyp is meant a circumscribed, rounded, often pedunculated tumour, distinguished from the more broad-based papilloma.

Adenoma

As used in the present study (but not always in quotations of other authors) covered

- a) adenomatous polyps,
- b) adenovillous polyps, and
- c) adenovillous papillomas.

For definition of the latter (a, b and c), see classification in chapter V.

BEN

Benign Epithelial Neoplasms. A term that is synonymous with adenoma in the sense used above.

(Adeno)villous lesions is to be understood as adenovillous polyps and adenovillous papillomas taken together.

Carcinoma

Unless otherwise stated, only used for colorectal adenocarcinoma. Diagnosis required at least the appearance of an unequivocal, irregular atypical epithelium forming cribrous structures, or invading through the basal membrane or otherwise invasion by the epithelium

through the muscularis mucosae. The term carcinoma in situ has not been used, and lesions not filling the above criteria have been grouped together with benign polyps.

Large bowel

Means colon and rectum.

Colon

The part of the large bowel situated above the promontory. In the necropsy series (I) - the borderline between colon and rectum is less distinct.

Right colon

Caecum, ascending colon, hepatic flexure, transverse colon.

Left colon

Splenic flexure, descending colon, sigmoid colon.

Rectum

That part of the large bowel situated below the promontory. Regarding the necropsy series (I), see above.

Synchronous
multiple
tumours

Tumours found at the same time in any one patient.

Metachronous
tumours

Tumours found on different occasions in any one patient.

Incidence

The average annual number of new cases diagnosed per 100,000 inhabitants of the population-at-risk.

Significance

Throughout this investigation $p < 0.05$ was considered significant.

IV

OCCURRENCE OF CARCINOMA AND BENIGN POLYPS

(I, II, III)

The number of patients with carcinoma and/or benign polyps and the sub-site-distribution of the lesions were studied in a clinical series (II, III) and in a necropsy series (I).

CLINICAL SERIES - MATERIAL AND METHODS

During a 10-year period (1958 to 1967, inclusive,) all together 960 new cases of colorectal carcinoma were treated at the Department of Surgery. Cases with adenocarcinoma on the basis of familial adenomatosis (10 cases) or ulcerative colitis (5 cases) were not included. During the period of investigation all together 1,231 cases of colorectal carcinoma were diagnosed in the town. Of these, however, 230 were diagnosed at necropsy only. The patients in the clinical series constituted 94 % of all cases diagnosed intra vitam. Those few not included had been cared for outside the Surgical Department and were, as a rule, inoperable.

NECROPSY SERIES - MATERIAL AND METHODS

During a 3-year period (Sept. 1, 1958 to Aug, 31, 1961) all together 3,398 subjects were necropsied at the Department of Pathology, but only the 3,041 subjects above 1 year of age were considered (see comments). All the protocols were perused by the

author and all colon-rectum tumours were recorded. Also the reports of the histopathological examination of the surgical specimens from subjects who had earlier undergone resection of the colon were studied.

RESULTS

Incidence of carcinoma.

The patients included in the clinical series (II) represented an average annual incidence of 40/100,000 inhabitants. When all carcinomas, diagnosed only post mortem were included, the figure was 52/100,000.

During the period covered by the investigation all together 12,718 necropsies were performed at the Department of Pathology. The frequency of patients with carcinoma of the colon and rectum not diagnosed before necropsy was 1.65 %. Assuming the same rate of such silent tumours among those inhabitants who had died but not been examined post mortem, the incidence of colorectal carcinoma in the population-at-risk would be 56.8/100,000 (II).

Frequency of cases with carcinoma.

In the necropsy series (I) 180 (5.9 %) cases of carcinoma were found.

Frequency of cases with multiple carcinomas. In 14 of the cases in the necropsy series (I) more than one colorectal carcinoma was demonstrated (see comments). Seven of these cases had earlier been operated on. In the clinical series (III) 44 patients (4.6 %) had multiple synchronous carcinomas.

Frequency of cases with benign polyps.

In the necropsy series (I) at least one benign polyp was found in each of 380 (12.5 %) cases (Table I).

The frequency of benign polyps in cases with coexisting carcinoma was higher. Thus, at least one benign polyp was found in 25.6 % of the 180 cases with carcinoma in the necropsy series (I) and in 22.2 % of the 960 patients with carcinoma in the clinical series (II). Among the patients with multiple carcinomas in the clinical series (III), benign polyps were found in as many as 28 (63.6 %) (Table I).

	CLINICAL SERIES	NECROPSY SERIES
UNSELECTED	—	12.5%
IN CASES WITH CARCINOMA	22.2%	25.6%
IN CASES WITH MULT. CARCINOMAS	63.6%	—

Table I. Frequency of cases with polyps.

Table II gives the frequency of cases with solitary and multiple polyps, respectively. Multiple polyps were more common in patients with carcinoma, especially in patients with multiple carcinomas.

		CLINICAL SERIES	NECROPSY SERIES
UNSELECTED	SOLITARY POLYPS	—	6.8%
	MULTIPLE POLYPS	—	5.7%
IN CASES WITH CARCINOMA	SOLITARY POLYPS	11.5%	10.0%
	MULTIPLE POLYPS	10.7%	15.6%
IN CASES WITH MULT. CARCINOMAS	SOLITARY POLYPS	15.9%	—
	MULTIPLE POLYPS	47.7%	—

Table II. Frequency of cases with solitary and multiple polyps, respectively.

Age- and sex-distribution.

The age- and sex-distribution of patients with carcinoma and benign polyps, respectively, in the two series (I, II) are given in Figs. 1 - 4. Fig. 5 illustrates the various male/female ratios. No sex-difference was found for patients with carcinoma only, but benign polyps were preponderant in males. Multiple lesions occurred about twice as often in males as in females.

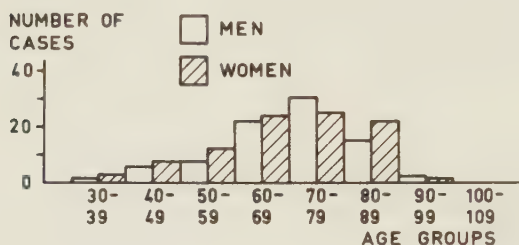


Fig. 1. Age- and sex-distribution of cases with carcinoma in the necropsy series (I).

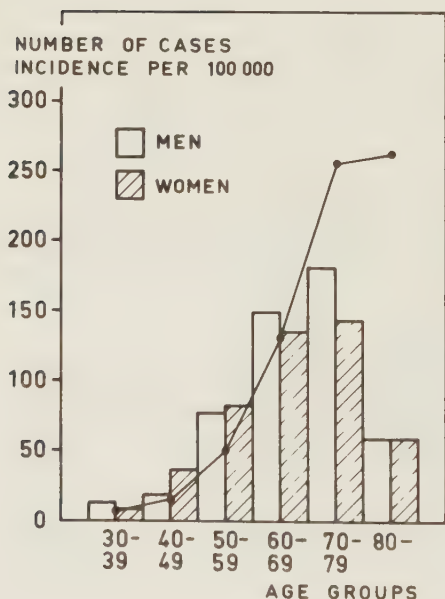


Fig. 2. Age- and sex-distribution and incidence of patients with colorectal carcinoma in the clinical series (II).

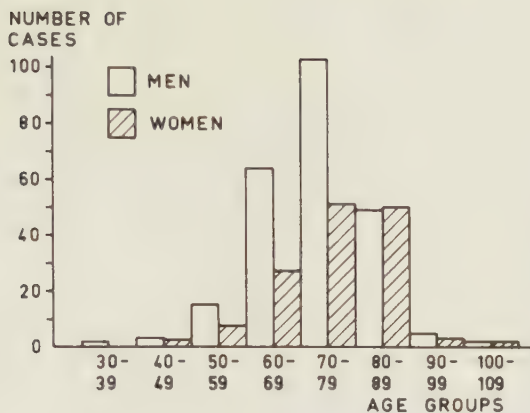


Fig. 3. Age- and sex-distribution of cases with benign polyps in the necropsy series (I).

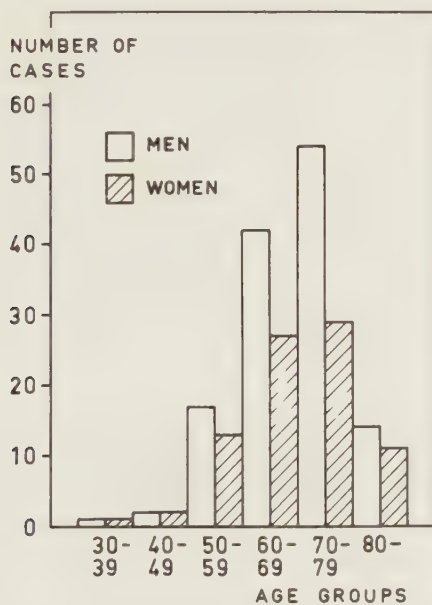


Fig. 4. Age- and sex-distribution of patients with benign polyps in the clinical series (II).

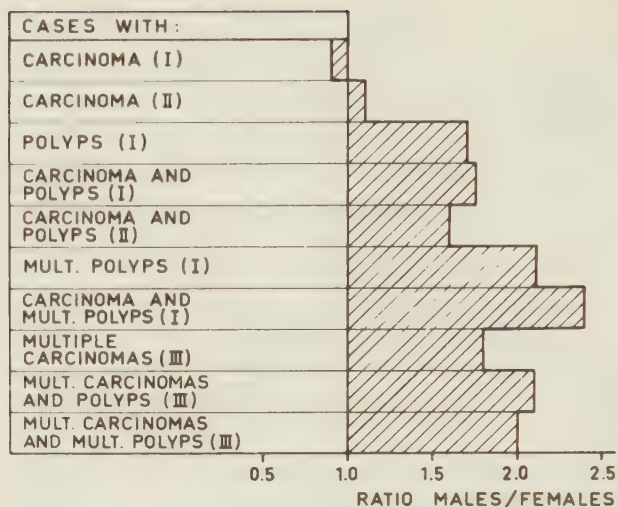


Fig. 5. Male/female ratios within various combinations.

Sub-site distribution of carcinomas.

The distribution of carcinomas among segments in the necropsy series is apparent from Fig. 6. Both the frequency distribution of all lesions and that of solitary lesions alone are given (see comments). The sites of two of the lesions were not known. Of those, whose sites were known, 23 % were situated in the rectum, 40 % in the sigmoid colon and 23 % in the caecum or ascending colon (compare Table V in the appendix).

In the clinical series (II) the sites of all the 1,009 lesions were known: 38 % were situated in the rectum and 29 % in the sigmoid colon. The caecum and ascending colon harboured 17 % of the lesions. This is shown in Fig. 7, which also gives the distribution of solitary lesions (compare table VI in the appendix).

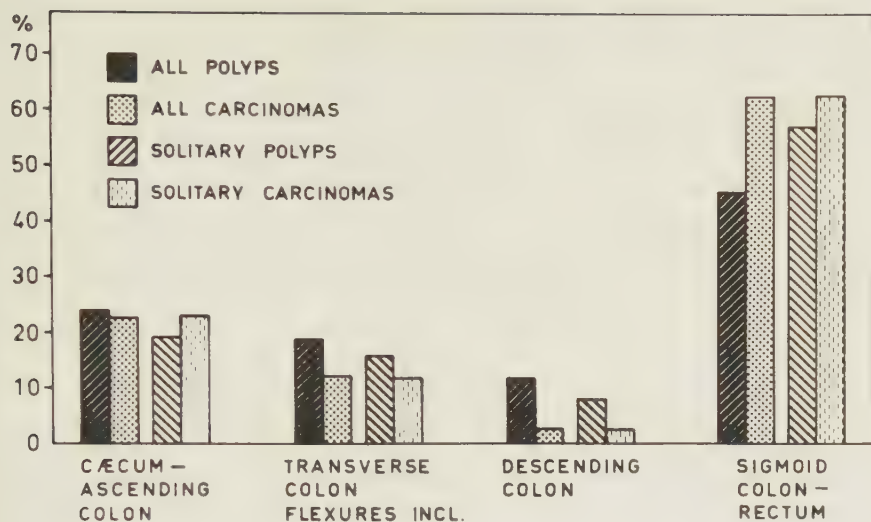


Fig. 6. Frequency-distribution of benign polyps and carcinomas, divided into that of all lesions, and that of solitary lesions only. Necropsy series (I).

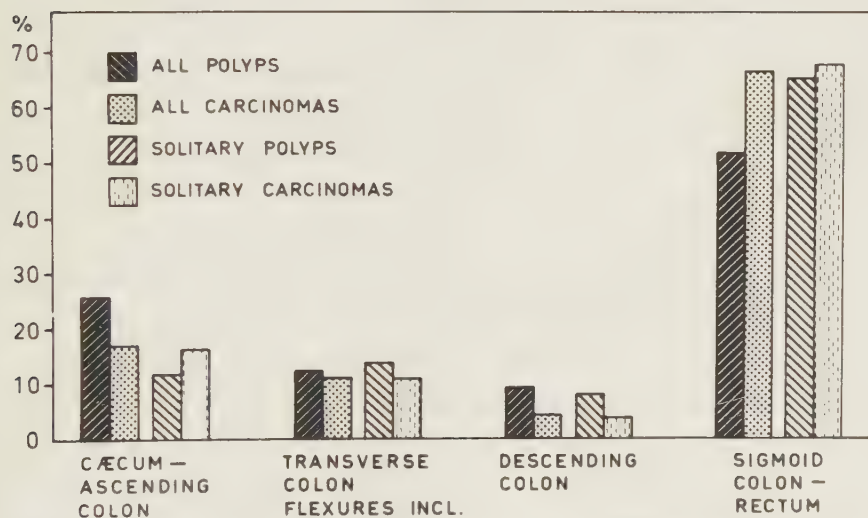


Fig. 7. Frequency-distribution of benign polyps and carcinomas, divided into that of all lesions, and that of solitary lesions only. Clinical series (II).

Sub-site distribution of benign polyps.

The distribution of the benign polyps among segments in the necropsy series (I) is apparent from Fig. 6. The sites of 466 of the 498 polyps found were known: 16 % were found in the rectum and 29 % in the sigmoid colon. The caecum and ascending colon harboured 24 % of the polyps. The distribution of solitary polyps is also shown in Fig. 6.

In the clinical series (II) the sites of 421 of the 456 polyps were known: 27 % were found in the rectum, 25 % in the sigmoid colon and 26 % in the caecum or ascending colon. This is seen in Fig. 7, which also shows the distribution of solitary polyps. (Figures are given in Table VII in the appendix).

In both series the segments most commonly involved by polyps as well as by carcinomas were the rectum and sigmoid colon. Analysis of the clinical series showed that coexisting polyps and carcinoma tended to be situated in the neighbourhood of each other. (See Figs. 30-38 in the original publication - II).

Size of benign polyps and polypoid carcinomas.

In the clinical series (II) the sizes of 407 of the 456 benign polyps could be estimated and of all the 92 carcinomas that had a polypoid shape. Table III gives the distribution of benign and malignant polypoid lesions according to size. No carcinoma less than 5 mm was found. Of the polypoid lesions above 10 mm (but less than 50 mm) in size, 59.0 % were malignant.

SIZE OF POLYP mm	NUMBER OF POLYPS	BENIGN	MALIGNANT
< 5	288	288 100 %	— —
5-10	77	64 83.1 %	13 16.9 %
> 10	134	55 41.0 %	79 59.0 %

Table III. Polypoid lesions of different size, divided into benign and malignant groups.

COMMENTS

The necropsy series included lesions found at earlier operation for carcinoma (89 cases), i.e. the entire large intestine was analysed. It seems probable that most carcinomas that had developed during life were included. It is not known whether this holds also for benign polyps, since information about earlier excision of small polyps might sometimes have escaped detection or be missing. The age-group 0-1 years was excluded in an attempt to exclude most juvenile polyps.

The basic publication of the necropsy series (I - Table 2) does not give full information about multiple malignant lesions since multiple carcinomas within any one segment were noted as a single lesion. This thesis gives the sub-site distribution of all carcinomas, as well as that of solitary lesions alone. To improve comparability with the clinical series, three cases with carcinoma on the basis of ulcerative colitis were excluded (three males without coexisting polyps).

The benign polyps were in this chapter reported regardless of histological diagnosis, since a study of the overall occurrence of gross polyps was considered valuable from a practical point of view. In the necropsy series, histological examination of polyps had not been performed routinely, but always when malignancy had been suspected. In the following chapter the benign polyps in the clinical series are reported according to histological types as well.

CONCLUSIONS

The present part of the investigation appears to warrant the following conclusions, regarding colorectal tumours in the population of Malmö:

- a) The average annual incidence of adenocarcinoma (cases diagnosed intra vitam) is about 40/100,000.
- b) The frequency of cases of carcinoma demonstrable at necropsy is 5.9 % and that of polyps 12.5 %.
- c) Benign polyps are more common in patients with carcinoma, especially if there are multiple carcinomas, than in the absence of carcinoma.
- d) The rectum and sigmoid colon together is the part most commonly involved by polyps and by carcinoma. The sub-site frequency distribution of solitary benign polyps is largely the same as that of solitary carcinomas, but when also multiple lesions are considered the distribution of benign polyps is relatively more even than that of carcinomas.
- e) Coexisting benign polyps and carcinomas tend to be situated near to each other.
- f) Men are more prone to develop polyps, especially multiple polyps, than women.

VARIOUS HISTOLOGICAL TYPES OF BENIGN POLYPS COEXISTING WITH CARCINOMA

(IV)

MATERIAL AND METHODS

The material consisted of the 381 polyps (in 110 men and 73 women) in the clinical series, where histopathological specimens were available. All the sections, stained with haematoxylin and eosin, were re-examined twice by one pathologist. Good agreement was found between the results of the two re-examinations (IV).

Classification.

Three morphological groups of polyps were distinguished, namely benign epithelial neoplasms (BEN), metaplastic polyps and miscellaneous polyps.

Three types of BEN were distinguished, namely

- a) pure adenomatous polyps, which have a polypoid shape, a smooth surface configuration, and are built up of closely packed glandular tubules (Fig. 8),
- b) adenovillous polyps, which have similar features except that the surface configuration is mainly villous (Fig. 9), and
- c) adenovillous papillomas, which are mainly sessile tumours with a basically papillary structure and usually a villous surface (Fig. 10).

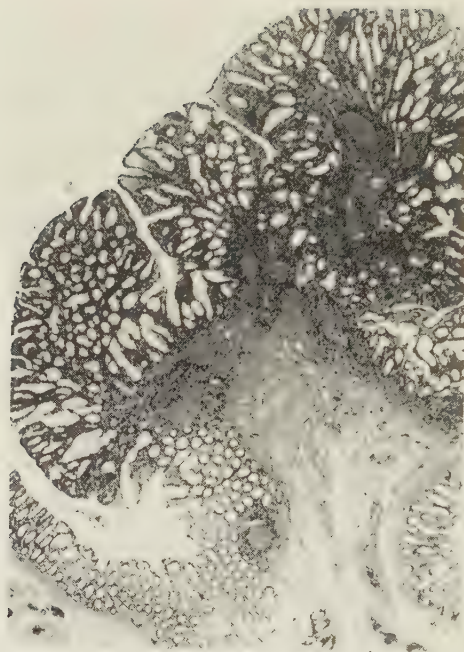


Fig. 8. Adenomatous polyp (Htx-eos x 15).

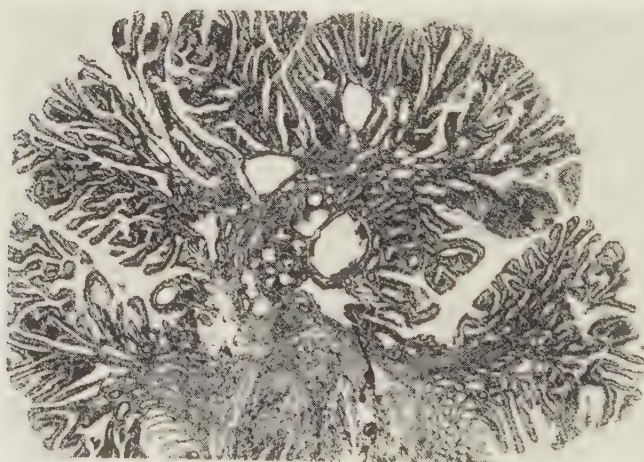


Fig. 9. Adenovillous polyp (Htx-eos x 11.5).

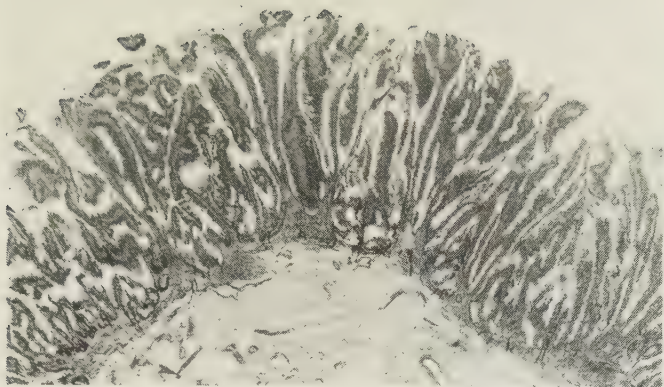


Fig. 10. Adenovillous papilloma (Htx-eos x 15).

BEN were classified according to six grades of differentiation, high, high to moderate, moderate, moderate to low, low, and as advanced dysplasia. For detailed definition of these grades reference is made to the basic publication (IV). Briefly, in the high grade group (Fig. 11) the glands and the epithelium closely resembled the normal mucosa. In the low grade (Fig. 12) there was an atypical and basophilic columnar epithelium without secretion vacuoles. There was a slightly irregular nuclear polarity and a markedly increased number of mitotic figures. In the grade labelled advanced dysplasia (Fig. 13) the cellular atypia was such as to suggest carcinoma. A diagnosis of carcinoma, however, required at least unquestionable epithelial irregularity or so called cribriform formations (see definitions). Tumours with varying grade of differentiation were classified according to the lowest grade found.

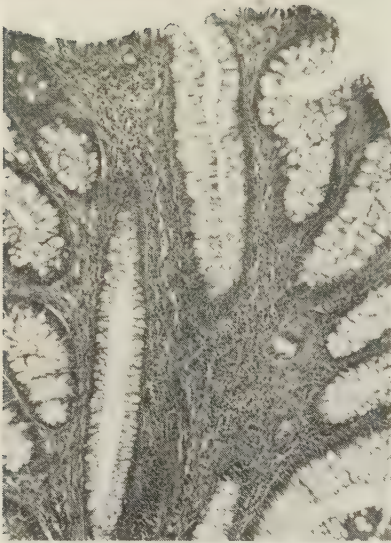
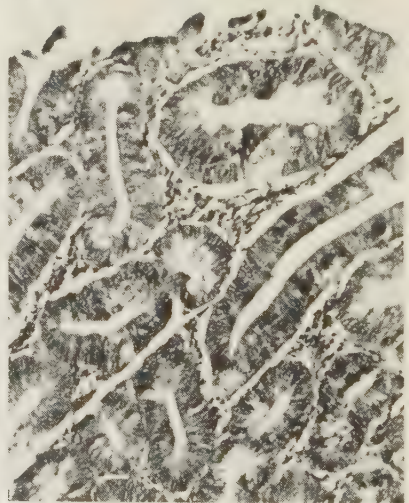
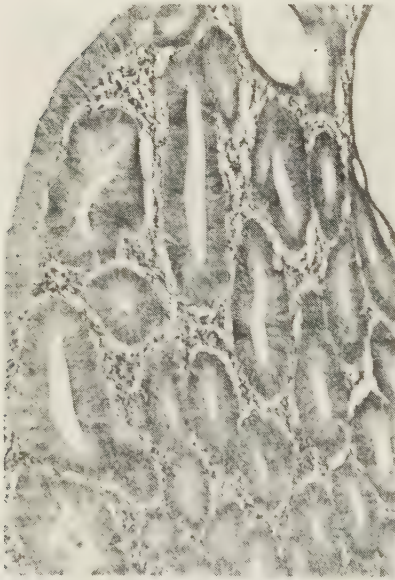


Fig. 11 (left). Example of BEN with high grade of differentiation (Htx-eos x 75).

Fig. 12 (left below). Example of BEN with low grade of differentiation (Htx-eos x 128).

Fig. 13 (right below). Example of BEN with advanced dysplasia (Htx-eos x 136).



RESULTS

All polyps.

Of the 381 polyps analysed, 81 % were BEN, 12 % were metaplastic and 7 % were of miscellaneous types.

Benign epithelial neoplasms (BEN).

Some patients had more than one type of lesion. The number of patients with at least one BEN was 174 (18 % of the 960 patients with carcinoma). The male/female ratio was 1.6. Fig. 14 gives the morphological classification and sex-distribution of BEN. Almost one fourth of all BEN were adenovillous. Table IV gives the site distribution of BEN, divided into that of

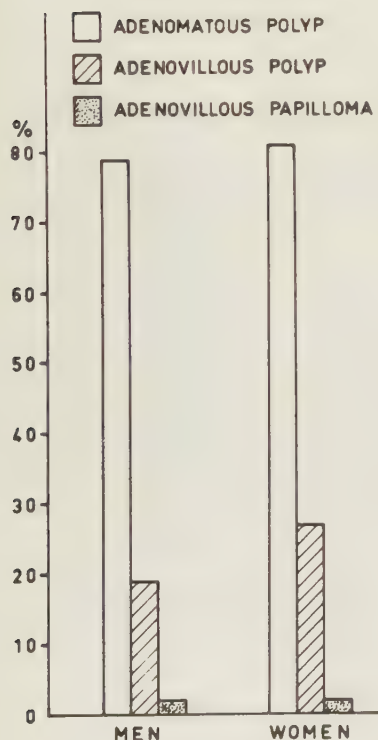


Fig. 14. Frequency-distribution, in each sex, for adenomatous polyps, adenovillous polyps, and adenovillous papillomas, respectively.

SITE	ADENOMATOUS POLYP		ADENOVILLOUS POLYP OR PAPILLOMA		METAPLASTIC POLYP	
	NUMBER	%	NUMBER	%	NUMBER	%
CÆCUM	14	6	4	6	1	2
ASCENDING COLON	61	26	16	23	3	7
TRANSV. COLON (FLEXURES INCL.)	27	11	8	11	3	7
DESCENDING COLON	22	9	7	10	—	—
SIGMOID COLON	63	27	15	21	10	22
RECTUM	51	21	20	29	28	62

Table IV. Sub-site distribution of adenomatous polyps, adenovillous lesions, and metaplastic polyps, respectively.

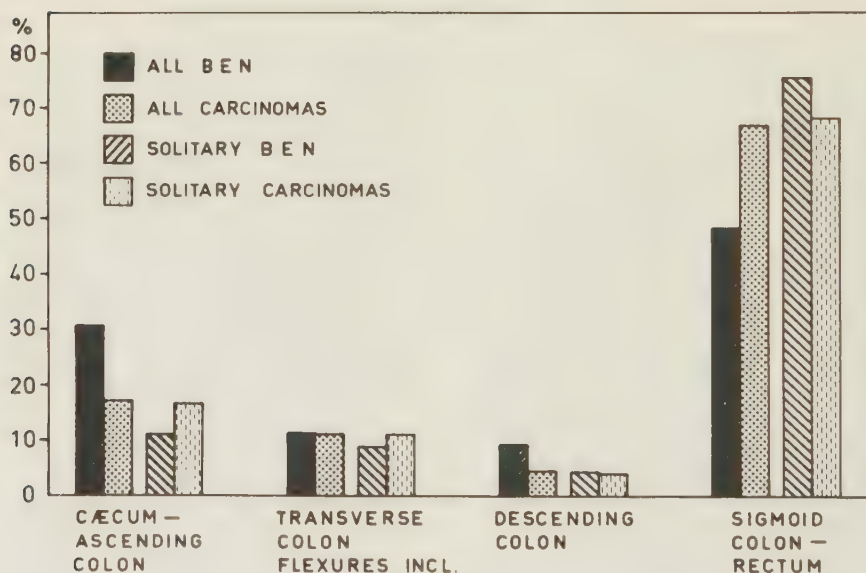


Fig. 15. Frequency-distribution of BEN and carcinomas, divided into that of all lesions, and that of solitary lesions only. Clinical series (II, IV).

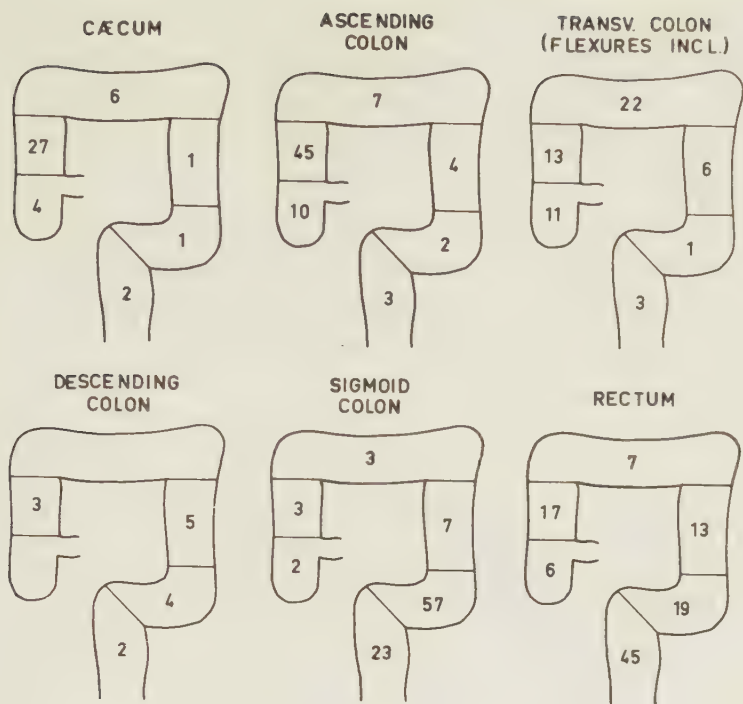


Fig. 16. Localisation of BEN according to localisation of coexisting carcinoma. In cases of multiple carcinomas in different segments the coexisting BEN is depicted in each segment affected by carcinoma.

adenomatous polyps and adenovillous lesions. The site distributions of these two groups of lesions were similar. In men, however, 54 % of the BEN were seen in the sigmoid colon and rectum, compared with only 38 % in the women. Fig. 15 compares the site distribution of BEN and carcinoma. Solitary lesions (compare Table VI and VII in the appendix) are reported separately.

It is clear that solitary lesions were equally distributed. When all lesions were considered, i.e. solitary and multiple lesions taken together, the frequency distribution of BEN was somewhat more even than that of carcinoma.

Fig. 16 shows the distribution of BEN according to the site of the coexisting carcinoma. It is clear that the BEN tended to be situated in the vicinity of the coexisting carcinoma.

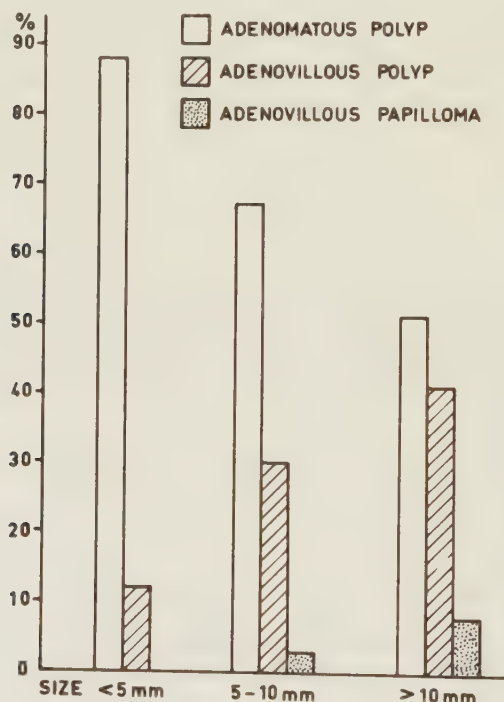


Fig. 17. Frequency-distribution of adenomatous polyps, adenovillous polyps, and adenovillous papillomas respectively, among size-groups.

In Fig. 17 the tumours are grouped according to size and morphological type. Adenovillous lesions were relatively more common among the larger lesions. In Fig. 18 adenomatous polyps and adenovillous lesions are distributed according to grade of differentiation. Most (77 %) of the adenovillous lesions belonged to the lower grades. 65 % of all BEN in men and 57 % in women belonged to lower than moderate grade.

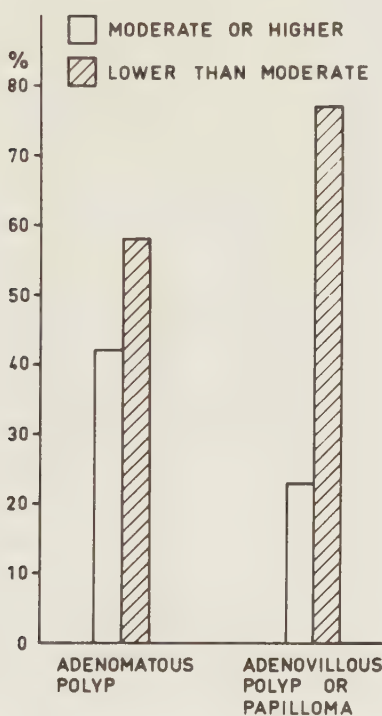


Fig. 18. Frequency-distribution of adenomatous polyps and adenovillous lesions according to grade of differentiation.

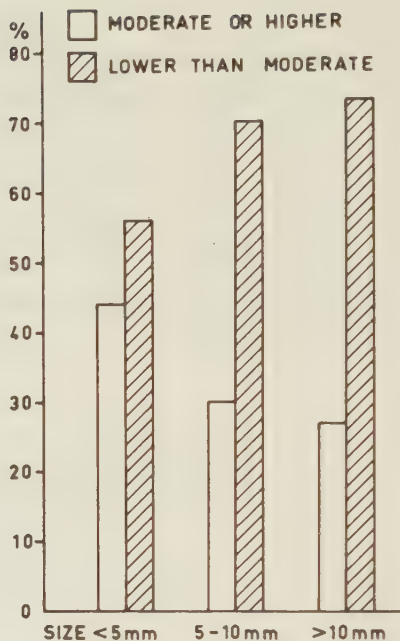
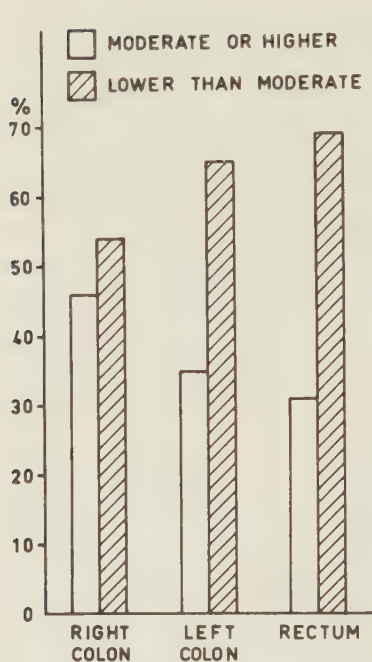


Fig. 19 (left). Frequency-distribution of BEN in right colon, left colon and rectum, respectively, according to grade of differentiation.

Fig. 20 (right). Frequency-distribution of BEN of various grades of differentiation, according to size.

The differentiation of BEN tended to decrease the nearer the lesion was to the anus (Fig. 19), and the larger the lesion was (Fig. 20).

37 % of BEN in the same segment as the coexisting carcinoma, 29 % of those in an adjacent, and 27 % of those in other segments were either poorly differentiated or showed advanced dysplasia.

Metaplastic polyps.

46 metaplastic polyps were found in 26 patients (male/female ratio 1.4). None of the lesions were found in patients below 50 years of age. The sub-site distribution is given in Table IV. With but one exception the metaplastic polyps were less than 5 mm in diameter.

COMMENTS

The analysis reported in chapter IV included all benign polyps. It is well known that polyps occurring in the large bowel are not always epithelial, e.g. lipomas and inflammatory polyps. Such lesions have never been thought to be precursors of adenocarcinoma. Neither is there evidence that metaplastic polyps have any pre-malignant potential, and Morson (1962) has therefore regarded them as non-neoplastic. Metaplastic polyps are generally said to be tiny lesions, found mostly in the rectal mucosa. However, it is only during the past few years that attention has been drawn to the innocent character of metaplastic polyps (Morson, 1962; Arthur, 1962; Lane & Lev, 1963). As in most earlier polyp-series, these polyps were therefore included as adenomas in the present series (I, II, III) reported on in chapter IV. It nevertheless seemed reasonable to consider adenomas separately in pathogenetic evaluations. Instead of the term adenoma, the synonymous term BEN was used here, in an attempt to avoid misunderstanding. The name adenoma is namely often used to describe the adenomatous polyp and sometimes, in the scope of the term, adenovillous papillomas are included.

Several authors have classified BEN according to their grade of differentiation (e.g. Schmieden and Westhues, 1929; Pagtalunan, 1965; Andreassen, 1969; Potet & Soullard, 1971, and others). However, no generally accepted classification exists. The classification used here is adopted from that of the Department of Pathology in Malmö, and is fairly similar to that used by Potet and Soullard, for instance.

The analysis of the differentiation of BEN according to the distance from the coexisting carcinoma was confined to solitary lesions and since the number was small, the results should not be regarded as conclusive.

CONCLUSIONS

The present part of the investigation appears to warrant the following conclusions, regarding benign polyps, detected by routine methods, and coexisting with carcinoma, in the population of Malmö:

- a) Of all polyps, about 80 % are BEN.
- b) The rectum and sigmoid colon is the part most commonly involved by BEN and by carcinoma. The sub-site frequency distribution of solitary BEN is similar to that of solitary carcinomas, but when also multiple lesions are considered the distribution of BEN is relatively more even than that of carcinoma.
- c) BEN tend to be located in the vicinity of the coexisting carcinoma.

- d) The average grade of differentiation of BEN situated in the left colon and rectum tends to be lower than of BEN in other segments.
- e) The average grade of differentiation tends to vary inversely with the size of BEN.
- f) Villous lesions tend to be larger and, on the average, less well differentiated than adenomatous polyps.
- g) Most BEN are found in men.
- h) Metaplastic polyps are found mostly in the rectum and sigmoid colon, and rarely exceed 5 mm in diameter.

VI

THE RISK FOR DEVELOPMENT OF SUBSEQUENT BENIGN AND MALIGNANT TUMOURS IN PATIENTS WITH POLYPS

(V)

MATERIAL AND METHODS

For this part of the investigation, all patients in the town of Malmö, who in a three year period (1955-1957) had a colorectal polyp ("index-polyp") radiologically diagnosed by the double contrast method ("index-roentgen") and meeting certain criteria (described in detail in the original publication - V), were reevaluated after an average period of ten years (never less than five years), in order to ascertain whether any new polyp or carcinoma had developed. This "polyp series" (123 patients), was compared with a "control series" evaluated according to the same principles. The controls consisted of sex- and age-matched patients, in whom radiographic examination of the colon and rectum in 1955-1957 was normal.

All patients who belonged to the polyp series or the control series and who had not undergone reexamination of the colon and rectum at least five years after the index roentgen, were invited to have a new examination with a double contrast roentgenography and rectoscopy. If the patient had died five years or more after the index roentgen, the necropsy protocol was reviewed and specimens were re-examined histopathologically. A polyp, demonstrated at an examination after the index roentgen was accepted as new if

it had been observed at least twice at repeat roentgen examinations, verified by biopsy, or seen at necropsy. Whenever a new polyp was detected previous roentgen films were reexamined to check that the polyp had not been present already at index roentgen examination. All specimens available were histopathologically re-examined and classified according to uniform criteria, as described in chapter V.

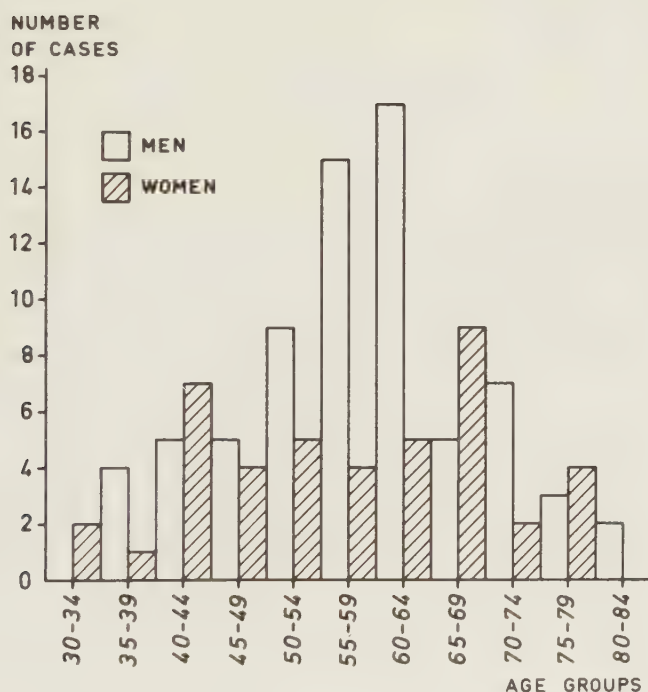


Fig. 21. Age- and sex-distribution of the 115 patients with "index polyps" (equals that of the controls).

As reported in the original publication (V), the number of patients with new polyps, irrespective of histological type, found in the polyp series was significantly larger than in the control series. In the present context the material is confined to that analysed after exclusion of such polyps which histopathological examination had shown to be of metaplastic or non-epithelial type. After these exclusions, 115 patients meeting the criteria were left for analysis. The age- and sex-distribution is shown in Fig. 21. The peak occurred in the age group 60-64 years, but the median age was 55. The male/female ratio was 1.7.

RESULTS

At index roentgen examination, 35 patients of the polyp series had more than one polyp, and all together 175 polyps were found in the 115 patients. The distribution of the polyps in the large intestine is shown in Fig. 22 a. The sigmoid colon and the rectum were the sites of 70 % of these polyps. New polyps occurred in 24 patients (male/female ratio 2.0) after an average of 102 months. Nine of these 24 patients had had more than one index polyp. In 14 cases the new polyp was examined histologically (adenomatous polyps in 12 cases and adenovillous polyps in two). Seven of the 24 patients developed more than one new polyp, and all together 39 new polyps were found. Their distribution is given in Fig 22 b. The left hemicolon and the rectum harboured 59 % of these polyps. Carcinoma of the large intestine developed in three of the patients.

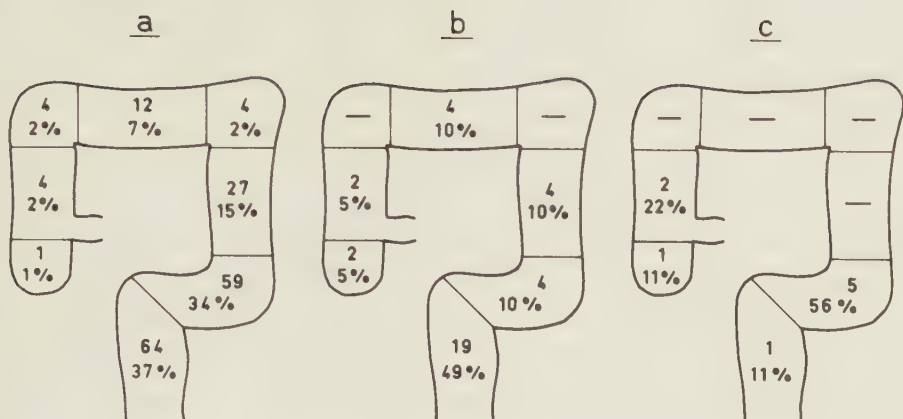


Fig. 22. Distribution of polyps in the large intestine
a) index polyps
b) new polyps in polyp series
c) new polyps in control series.

In the control series eight (male/female ratio 1.0) of the 115 patients developed polyps, which were detected after an average period of 98 months. Two new polyps occurred in one patient. Distribution of the new polyps in the control series is given in Fig. 22 c. Six of the new polyps were found in the sigmoid colon and rectum. Microscopic analysis, performed in only two of these eight patients, proved the polyps to be adenomatous. No carcinoma occurred in the controls.

The difference between the number of patients with new polyps found in the polyp series and in the control series was statistically significant. The mean observation time of the two series was 126 and 118 months, respectively, and the median observation time

was 133 months in both series. The number of carcinomas (3) found in the polyp series was too small to permit statistical analysis.

COMMENTS

The series presented is basically a radiographic one. With the technique used even very small lesions (< 5 mm) can be detected (Andr  n et al., 1955). To avoid false positive diagnosis, no polyp was recorded as such unless it was demonstrated twice, or verified by other means. The criteria thus were used in order to obtain as firm a diagnosis as possible, and these limitations explain why the number of patients accepted for analysis was rather small. Because of the type of material it was not possible to obtain a histologic diagnosis of all polyps (many lesions were not removed). Those available were evaluated by uniform criteria. Of the initial index polyps available for histologic examination, 86 % were BEN. This figure compares well with 81 % in the series presented in chapter V and there seems to be no reason to believe that the frequency of polyps, other than BEN, was higher among those not analysed microscopically.

CONCLUSION

It appears warranted to conclude that the presence of one or more benign colorectal polyp implies an increased risk of the patient developing new polyps (and, despite the meagreness of evidence, possibly also carcinoma).

VII

GENERAL DISCUSSION

The treatment of polypoid colorectal lesions frequently offers practical problems. Early removal of small carcinomas or lesions known to be potentially malignant is imperative, but removal of innocent lesions only involves an unnecessary risk of surgical complications. Increased knowledge of the significance of polypoid lesions is therefore highly desirable from a practical as well as from a theoretical point of view. Opinions differ regarding the relationship between benign polyps and carcinoma (the "adenoma-carcinoma sequence"). Some authors, like Castleman & Krickstein (1962) and Horn (1971), agree with the conception presented by Spratt, Ackerman & Moyer (1958) that "the theory of origin of adenocarcinomas of the colon within adenomatous polyps has little to support it". Others, like Helwig (1947) and Morson & Bussey (1970), believe that a relationship does exist.

The present material is almost complete regarding persons consulting the hospital. Furthermore, the high rate of necropsy of all persons who have died in the town provides a good estimate of the disease also among those who had not attended the hospital.

It was thus possible not only to report the number of patients with carcinoma diagnosed intra vitam or post mortem, but also to estimate the true incidence of colorectal carcinoma in a defined population (II).

Such knowledge provides essential information for pathogenic discussions of colorectal carcinoma. For comparisons with incidence figures in national cancer registers in other geographical areas, where the necropsy rates are lower and notifications are based mainly on cases diagnosed intra vitam, the corresponding present incidence figure (i.e. in the clinical series, II) is probably preferable. The figure for the expected overall incidence, however, allows an estimate of the degree of selection.

For comparisons of incidence between countries the figures must be adjusted to a standard reference population. Thus, when the incidence figure for carcinoma found in the present clinical series (40.2/100,000) is adjusted to the "world population", used by UICC (Cancer Incidence in Five Continents, 1970), it will be 26.6/100,000 (II). This is nearer to the high figures reported from the West than to the low ones reported from the East (compare table XX and XXI in the basic publication - II). In other words, the population of Malmö is a fairly high-risk-population (for colorectal carcinoma).

Since benign polyps are not notifiable to cancer registries their corresponding incidence is not known, but some reports indicate that benign polyps are uncommon in populations with low risk of carcinoma (Bremner & Ackerman, 1970; Correa, Cuellar & Haenszel, 1972). Therefore, the "adenoma-carcinoma-sequence" should be analysed in both low- and high-risk populations, and in comparisons the risk-type of populations in question, must be considered.

The results of the present study will be compared mainly with those obtained in high-risk populations, viz. USA and Western Europe.

No data on the annual incidence of benign polyps are given in the present series, but the frequency of cases in which polyps were found at necropsy was 12.5 %. In the present investigation only routine methods were used for examination of the large bowel. In the literature the figures given for the frequency of patients with benign polyps vary considerably and much more than those given for carcinoma. This variation certainly depends upon, among other things, the examination methods used. For instance, Lawrence (1936) found polyps in 2.4 % of 7,000 cases in an ordinary necropsy series, while Atwater & Borgen (1945), who used a magnifying glass, found polyps in 69 % of 241 cases at necropsy. A more common figure, corresponding to that in the present series, is that reported by Helwig (1947) viz 9.5 % and that (10 %) found in an earlier necropsy survey in Malmö (Winblad & Frieberg, 1956). It seems natural that the frequency of cases with detected polyps should be highest in necropsy series, since such series presumably include most polyps that have developed during life, while clinical series include only those that have developed by the age of the patient at the time of the particular examination.

From comparisons with other studies where special methods have been used, it is obvious that many small lesions in the present series must have escaped detection. However, there is reason to believe that

series with high frequencies of polyps include a considerable percentage of metaplastic (hyperplastic) polyps, Lane et al. (1971), for instance, having found in a series of polyps from symptomatic adults that 90 % of polyps at most 3 mm in diameter were metaplastic. Such lesions are considered non-neoplastic (Morson, 1962) and therefore without interest from a practical, as well as from a pathogenic, point of view.

In the present study it was found that benign polyps, irrespective of histologic type, were twice as common in the presence, as in the absence, of carcinoma. The histopathologic analysis showed that about 80 % of these polyps were BEN, i.e. the type of main interest for pathogenic evaluations, and the above conclusion held even when only BEN were considered. This finding is incompatible with that reported by Spratt et al. (1958), who denied the existence of any relationship between adenoma and carcinoma, for one thing, because they found that "the frequencies of occurrence of adenomatous polyps in cancerous and noncancerous colons of persons over 50 years of age were the same". However, the present results agree with those given in other reports, such as that by Rider et al. (1954). They found carcinoma to be five times as common in patients with polyps as in patients without. In comparisons it must be considered how the materials are selected. For instance, whether the basic material is a series of polyps, like that of Rider et al. (1954) or, a series of carcinomas, like the present clinical series. Rider et al., however, also presented data on the frequency of polyps in patients with carcinoma. These data were collected from the literature, and in

the 12 series compiled, the frequency of patients with polyps ranged from 7.9 % to 75.0 %. In only three of these series was the frequency lower than 25 %. The reported frequencies of patients with polyps in series of carcinoma thus varies to the same extent as those in unselected series, but they tend to be higher.

For comparisons between series the time of detection should also be defined, either by the patients' ages or by some other suitable reference. Thus, if clinical series include polyps detected in patients at repeated examinations during several years (Enquist, 1957) they are probably not comparable with series examined during other lengths of time. The present study was based on polyps occurring on two defined occasions, namely at necropsy (I) and, for the clinical series (II, III, IV) at the time of detection of the coexisting carcinoma. In addition, the age- and sex-distribution of the patients with polyps was given for comparison.

In the present series, it was sometimes difficult to determine the exact sub-site-location of the lesions, and since there are no distinct borderlines between the segments, lesions might have been erroneously referred to an adjacent segment. If, however, two adjacent segments be taken together, the magnitude of this possible error would be much smaller. This would for example, correct for differences in the level of borderlines between the rectum and sigmoid colon (see definitions). Thus, in the present clinical series (II) rectal polyps as well as rectal carcinomas were comparatively more common than in the necropsy series

(I), but when the rectum and sigmoid colon were taken together, there was no difference.

In both series (I, II) the frequency-distribution of solitary polyps was similar to that of solitary carcinomas. When solitary and multiple lesions were taken together the same pattern was seen, but the distribution of benign polyps was then relatively more even than that of carcinomas. The difference between the distribution of solitary and multiple lesions is difficult to evaluate, but it seems reasonable to assume that the differences found depended on a few cases with multiple polyps in any one segment. When only solitary lesions were considered the number of polyps (and carcinomas) equalled that of the patients.

The two series (I, II) thus closely resemble one another regarding the distribution of polyps as well as of carcinomas among different segments of the large intestine, besides which the pattern of the distribution of benign polyps resembled that of the carcinomas. The sub-site distributions found supports the assumption of a relationship between polyps and carcinomas. Another finding lending support to the same assumption was that in the clinical series, solitary as well as multiple polyps were often situated in the vicinity of the coexisting carcinoma (II). When only BEN were considered (IV), the same tendency was seen (Fig. 16). There might be a source of error relevant to this finding in that many patients had undergone resection, which permitted a more thorough examination of the excised specimen. But thanks to double contrast roentgenography and rectoscopy, also polyps in other

parts of the large intestine could be diagnosed with a fairly high degree of reliability.

The sub-site distribution of BEN only, was somewhat more even than that of all the benign polyps, in that 31 % of the BEN were found in the caecum and ascending colon and 48 % in the sigmoid colon and rectum. Though the relative distributions within the colon-rectum of BEN and carcinomas were thus not quite identical, they are regarded as similar enough to warrant assumption of an interrelationship, especially as there was no difference between the distribution of solitary BEN and solitary carcinomas. The opinion thus arrived at in the present study contrasts with that of Spratt et al. (1958), who stated that "the frequency distribution of adenomatous polyps and cancers are not homogenous". However, these authors used another approach. They presumed that all adenomatous polyps had an equal, if any, tendency to become malignant and since they found that polyps were not distributed randomly about, i.e. proximally or distally, to the associated carcinoma, they rejected the concept of a relationship. Further, in studies of distribution of polyps and carcinomas, they compared the frequencies of the respective lesions, per unit of length of fixed bowel and found the frequency of polyps to equal that of carcinomas in the caecum, be lower in the sigmoid colon and rectum, and higher in the rest of the colon. Finally, these authors admitted that adenovillous papillomas often contain infiltrative carcinoma and therefore excluded such lesions from their study.

Other authors have, however, reported adenomas and carcinomas to be equally distributed among segments and this was one of the reasons why Helwig (1947) assumed an intimate relationship between these lesions. As pointed out in the introduction, reported sub-site distributions of polyps vary with the type of material and the examination methods used. Thus clinical series often revealed most polyps in the rectum and sigmoid colon (Welch, 1964), while necropsy series often showed a more even distribution (Arminski & McLean, 1964). The variation of the examination methods used was greatest in clinical series. Some series, for instance, are based mainly on rectoscopy (Enquist, 1957), while others are based on radiography of the entire large bowel with the double contrast technique (Welin, 1967).

In the present investigation the concept of a relationship between BEN (adenoma) and carcinoma was strengthened by the findings made at histopathological study of the grade of differentiation of BEN. It was found that the grade of differentiation of BEN tended to be lowest in the left colon and rectum, i.e. where carcinomas were most common (IV). The finding might suggest an increased tendency of BEN to become malignant in these distal parts of the large bowel.

However, it must be remembered that no generally accepted grading system exists. On the contrary, opinions differ regarding borderlines between entirely benign adenomas, "carcinoma in situ" and frank carcinoma. Observations made by, among others, Hultborn (1954) suggested a gradual transition from one group

to another and to cancer. Potet & Soullard (1971) stressed the difficulty in distinguishing dedifferentiated polyps from those which show the picture of "true cytological cancer in situ". In the present study carcinoma was not diagnosed at the cytological level alone, but only on the histological level if at least so called cribriform formations were detected. But some authors, such as Morson & Dawson (1972), do not use the term carcinoma unless the growth has clearly infiltrated the muscularis mucosae. This might be legitimate from a practical clinical point of view, since it is widely accepted that lesions without invasion of the muscularis mucosae only rarely, if ever, set up metastases. But, as stated by Culp (1967), it is difficult to understand why in situ carcinoma in an adenomatous polyp should not be given the same respect as it would if discovered in any other epithelial structure. Morson & Bussey (1970), however, agree that any meaningful discussion of the pathogenesis and malignant potential of benign neoplastic polyps requires analysis of their grade of differentiation.

The grading used in the present investigation was an attempt to measure the cytological and histological changes seen. In the evaluation of the results it must be realized that the correlation to pre-malignant behaviour of the lesions is not definite even if it generally appears that pre-malignancy becomes morphologically more conspicuous with increasing loss of differentiation.

The histopathological analysis of the BEN coexisting with carcinoma in the present clinical series showed that villous lesions (adenovillous polyps and papillomas) not only tended to be larger, but also to have a lower grade of differentiation than adenomatous polyps. These findings are not conclusive, but they seem to suggest that lesions which are chiefly villous tend to be somewhat more closely related to carcinoma than are adenomatous polyps. This finding agrees with that of Andreassen (1969). He found that the risk of malignant degeneration tended to be increased when the polyps (not only papillomas) were chiefly villous. That adenovillous papillomas are closely related to carcinoma is not a matter of controversy. Thus Castleman & Krickstein (1962), who belong to those who deny that adenomatous polyps become malignant, agree that adenovillous papillomas have a high premalignant potential, as do Spratt et al. (1958). According to Castleman & Krickstein, the failure to distinguish these lesions from adenomatous polyps has led to exaggeration of the tendency of the latter to become malignant. But the concept that adenovillous papilloma is a disease distinguished from that of adenomatous polyps is not subscribed to by for instance Morson & Dawson (1972), who instead state that adenomatous polyps, adenovillous polyps and adenovillous papillomas are only terms used to describe different growth patterns of one disease with a wide range of appearances. Culp (1967) reported 7.5 % of the adenomatous lesions in his compilation to have villous features in part or throughout, but Fung & Goldman (1970), in a prospective analysis, showed that focal villous changes in adenomatous polyps were more common than

earlier believed. They found such changes in 35 % of solitary adenomatous polyps and in as many as 75 % of lesions larger than 10 mm in diameter. However, they stated that the evidence for obligatory transformation and increased malignant potential of the intermediate type (adenovillous polyps) was inconclusive.

In the present clinical series (II) of colorectal carcinoma all polypoid carcinomas and all coexisting benign polyps were compared according to size. No carcinoma smaller than 5 mm was found. Of polypoid tumours above 10 mm, 59 % were malignant. In the evaluation of these figures it must be borne in mind that the size in this investigation could not be measured exactly, but only estimated. The greatest problem was to classify polyps about 5 mm in size. Since all, except one, of the polypoid carcinomas were classified as Dukes' group A, this group apparently includes many lesions without invasion of the muscularis mucosae, and the frequency of polypoid carcinomas therefore is supposed to exceed that found by investigators who stipulate such invasion for diagnosis of carcinoma. But the histologic analysis of the present benign polyps reinforced the impression of a gradual transition to carcinoma, since it was found that 73 % of BEN above 10 mm in size showed one of the three lowest grades of differentiation, as compared with 56 % of those smaller than 5 mm. This trend is comparable with results presented by Culp (1967), based on a composite study of 1,510 polyps, of which 83 % were adenomatous in origin (Pagtalunan et al., 1965; Culp et al., 1966; Lescher et al., 1967; Wychulis et al., 1967). Many authors, such as Morson & Bussey (1970),

feel that size is an important factor in the malignant potential of neoplastic polyps, whether adenomatous or villous. A commonly reported risk level for frank carcinoma is 10-12 mm (Spratt & Ackerman , 1960; Wenckert, 1963; Welin 1968). From a practical point of view it is believed that at least lesions more than 10 mm in size should be excised.

The present finding that a higher frequency of patients with multiple carcinomas have polyps, and especially multiple polyps, than patients with a single or no carcinoma suggests that these patients have a tendency to develop benign and malignant colorectal tumours. The finding is in agreement with earlier reports by, among others, Thomas et al. (1948) and with the finding by Bussey et al. (1967) that patients operated on for colorectal carcinoma are exposed to an increased risk of developing a subsequent (metachronous) carcinoma and that the risk is higher if the patient has coexisting BEN of the large intestine.

Another indication of an increased tumour tendency was the finding that the presence of an adenoma implied a risk of new polyps. Similar results have earlier been reported by Rider et al. (1959) and Weakley & Swinton (1962). These studies were, however, based mainly on rectoscopic examinations, while the present study was based on radiography of the entire large bowel. Summing up, it is believed from a practical point of view that once a colorectal adenomatous or adenovillous lesion has been diagnosed, the patient should undergo examination of the entire large bowel for coexisting carcinomas, and if negative, the patient should

be followed up because of the tendency of new polyps to appear in these patients and of the possibility of the development of carcinoma. The results so far discussed appear to provide circumstantial evidence of a relationship between benign polyps and carcinoma.

In the present study there seemed to be a sex-difference in the tendency to develop tumours. It was namely found:

- a) that BEN, as well as carcinomas (II) in the rectum were more common in men than in women, and that if the rectum and sigmoid colon were taken together, BEN were still more common in men than in women,
- b) that the average grade of differentiation of BEN in patients with carcinoma seemed to be somewhat lower in men than in women,
- c) that men, as shown in Fig. 5, are preponderant among cases with polyps and especially among cases with multiple lesions. However, no sex-difference for patients with carcinoma was found.

These findings agree well with the theories proposed by Haenszel & Correa (1971; 1973) as an epidemiological model. That model was constructed from comparative geographic observations of incidence and sub-site distribution of colorectal carcinoma, from which it was "conjectured that the 'entity colonic cancer' may have at least two separate components: caecum-ascending colon and sigmoid-rectum. It is the latter which may be responsible for the enhanced risks observed in North America and Western Europe". This model, here somewhat abbreviated, is based on the following

findings, "a) in low-risk populations where the disease is 'endemic', colonic cancers are concentrated in the caecum and ascending colon, female cases are preponderant... b) When a new etiologic factor is introduced into such a population, the transition from an 'endemic' to an 'epidemic' phase is first expressed as a rise in sigmoidal cancers among men... c) A rise in female sigmoidal cancer follows later... d) As exposures to the etiologic factor become more intense and prolonged, a later phase is characteristically a rise in caecal- and ascending colonic cancers more marked for males than for females, so that the female excess in caecal cancer prevailing under 'endemic' conditions is diminished". Similar findings regarding geographic variation in sub-site distribution of carcinoma has been reported by deJong et al. (1972).

The findings in the present material, if applied to the model proposed by Haenszel & Correa, thus suggest that colorectal carcinoma is 'epidemic' in the population of Malmö and that there might exist an etiologic factor responsible for development of both BEN and carcinoma. This line of thought is not in conformity with the idea of Spratt et al. (1958) that all adenomatous polyps have the same tendency to become malignant (if they are pre-malignant at all), but it agrees with the following statement by Morson & Bussey (1970): "the possibility that the malignant potential of adenomas may vary with site (as well as other factors) must not be neglected when considering a possible relationship between adenomas and cancers. The real problem is not just whether all adenomas are pre-malignant, and if not all, which adenomas are pre-malignant".

Increased tumour-tendency may thus be explained by a common cause of BEN and carcinomas or by development of carcinomas from adenomas. In either case, the cause may be a constitutional disposition and/or carcinogenic substances present in the contents of the large intestine (Spratt & Watson, 1971). In this context it is interesting to note that it is experimentally possible to induce colorectal carcinoma as well as adenomas in the rat by injection of carcinogenic substances (Spjut & Spratt, 1965).

In the present series it was found that BEN located in the vicinity of the coexisting carcinoma were more often either low-grade differentiated or showed advanced dysplasia than BEN located elsewhere in the large bowel. This finding is by no means conclusive, but seems to illustrate a local tendency to tumour-development. The finding conforms with the finding of Culp et al. (1966) that in surgical specimens from patients operated on for carcinoma of the distal 25 cm of the large bowel, 37.3 % of coexisting adenomatous lesions showed the picture of carcinoma in situ (compare: advanced dysplasia), and also with the finding by Kalus (1972) that 47 % of adenomatous polyps in the same segment as a coexisting carcinoma were carcinoma in situ. The above findings in the present investigation also, in the epidemiologic context, agree with the "hit-theory" as applied by Hultborn (1954), and with the epidemiological hypotheses of Burkitt (1971). He assumes that if carcinogenic substances of any kind are formed in the contents of the large bowel, it is reasonable to believe that their action varies with the faecal transit time and with any regular arrest

in some part of the large bowel. According to Burkitt a low-residue diet leads to a prolonged transit time and causes faecal arrest and he concludes that such arguments "incriminating a fibre-deficient diet in the cause of bowel cancer is consistent with epidemiological and other findings (1972)".

VIII

SUMMARY AND CONCLUSION

A study of colorectal polyps and carcinoma, with special reference to their relationship was performed in the population of Malmö, which lends itself well to epidemiological studies. The town has a rather stable population of about a quarter of a million, and the medical service is confined to one general hospital. Collection of almost complete series was therefore possible. The study was based on three main series, namely:

- a) a three-year necropsy series of 3,398 consecutive post-mortem examinations, comprising 99 % of all hospital deaths,
- b) a ten-year clinical series of 960 cases of colorectal carcinoma, comprising 94 % of all cases diagnosed intra vitam in the town, and
- c) a three-year radiographic series with long term follow-up consisting of 123 patients with, and of an equal number of matched controls without, colorectal polyps.

The overall number, frequency and localisation of carcinomas and benign polyps, detected by routine methods were determined in the necropsy and clinical series. The clinical series was then subdivided for more detailed study of multiple colorectal carcinomas, and for a histopathological evaluation of benign polyps. The risk of patients with polyps developing new tumours, benign or malignant, was assessed in the radiographic series.

The findings of interest may be summarized as follows.

1. The average annual incidence of colorectal carcinoma, diagnosed intra vitam, was 40/100,000.
2. Benign polyps, of any type, as well as adenomas only (i.e. benign epithelial neoplasms - BEN), were more common in large intestines with carcinoma.
3. Benign polyps were most common in cases with multiple carcinoma.
4. Of all polyps, coexisting with carcinoma, about 80 % were adenomas (BEN).
5. The sub-site distribution of solitary carcinomas, solitary polyps of any type, and solitary adenomas (BEN), were similar.
6. The patterns of the sub-site distribution of polyps and of carcinomas were fairly similar when solitary and multiple lesions were taken together, even if carcinomas were then relatively more evenly distributed than carcinomas.
7. Benign polyps tended to be localised to the vicinity of a coexisting carcinoma.
8. Benign polyps (BEN) as well as carcinomas in the rectum were more frequent in men than in women.
9. Men were more prone than women to develop polyps, especially multiple polyps.
10. The grade of differentiation of adenomas (BEN), coexisting with carcinoma, tended to vary as follows:
 - a) the nearer the polyp to the anus, the larger the polyp and the nearer a solitary polyp to a coexisting solitary carcinoma, the lower the average grade of differentiation.

- b) the average grade of differentiation was lower if the lesion was adenovillous.
11. The presence of a colorectal polyp implied a risk of the patient developing new polyps.

CONCLUSION

The findings in the present study support the concept of a relationship between benign polyps (BEN) and carcinoma.

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REFERENCES

- Andreassen, J.C. 1969. Mucosal polyps of the colon and rectum. Classification and relation to carcinoma. (A study based on 9 years material with follow-up examination). Acta Chir Scand, Suppl. 396, 123-169.
- Andrén, L., Friberg, S. & Welin, S. 1955. Roentgen diagnosis of small polyps in the colon and rectum. Acta Radiol (Stockh) 43, 201-208.
- Arminski, T.C. & McLean, D.W. 1964. Incidence and distribution of adenomatous polyps of the colon and rectum based on 1000 autopsy examinations. Dis Colon Rectum 7, 249-261.
- Arthur, J.F. 1962. The significance of small mucosal polyps of the rectum. Proc R Soc Med 55, 703-704.
- Atwater, J.S. & Bargaen, J.A. 1945. The pathogenesis of intestinal polyps. Gastroenterology 4, 395-408.
- Bacon, H.E. 1971. Ten commandments for improving survival. Pa Med 74, 59-62.
- Berge, T. 1967. The metastasis of carcinoma with special reference to the spleen. Acta Pathol Microbiol Scand, Suppl. 188.
- Bjerre, B. 1969. Studies on population screening for early carcinoma of the uterine cervix. Acta Obstet Gynecol Scand 48, Suppl. 6.
- Bremner, C.G. & Ackerman, L.V. 1970. Polyps and carcinoma of the large bowel in the South African Bantu. Cancer 26, 991-999.
- Buntain, W.L., ReMine, W.H. & Farrow, G.M. 1972. Premalignancy of polyps of the colon. Surg Gynecol Obstet 134, 499-508.
- Burkitt, D.P. 1971. Epidemiology of cancer of the colon and rectum. Cancer 28, 3-13.
- 1972. Cancer of the colon and rectum. Epidemiology and possible causative factors. Minn Med 55, 779-783.
- Burns, F.J. 1966. The relationship between polyps and cancer of the colon and rectum. Dis Colon Rectum 9, 197-200.
- Bussey, H.J.R., Wallace, M.H. & Morson, B.C. 1967. Metachronous carcinoma of the large intestine and intestinal polyps. Proc R Soc Med 60, 208-210.

- Cancer incidence in five continents. 1970. Ed. by R. Doll, C. Muir & J. Waterhouse. International union against cancer (UICC), vol. 2. Springer-Verlag, Berlin, Heidelberg and New York.
- Cancer incidence in Sweden 1970. 1973. National board of health and welfare. The Cancer registry, Stockholm.
- Castleman, B. & Krickstein, H.I. 1962. Do adenomatous polyps of the colon become malignant? N Engl J Med 267, 469-475.
- 1966. Current approach to the polyp-cancer controversy. Gastroenterology 51, 108-112.
- Chapman, I. 1963. Adenomatous polypi of large intestine: incidence and distribution. Ann Surg 157, 223-226.
- Correa, P., Duque, E., Cuello, C. & Haenszel, W. 1972. Polyps of the colon and rectum in Cali, Colombia. Int J Cancer 9, 86-96.
- Culp, C.E. 1967. New studies of the colonic polyp and cancer. Surg Clin North Am 47, 955-960.
- Culp, C.E., Dockerty, M.B. & Jackman, R.J. 1966. Histopathology of satellite polyp. Arch Surg 92, 65-70.
- Dukes, C.E. 1932. The classification of cancer of the rectum. J Pathol Bacteriol 35, 323-332.
- Enquist, I.F. 1957. The incidence and significance of polyps of the colon and rectum. Surgery 42, 681-688.
- Fung, C.H.K. & Goldman, H. 1970. The incidence and significance of villous change in adenomatous polyps. Am J Clin Pathol 53, 21-25.
- Haenszel, W. & Correa, P. 1971. Cancer of the colon and rectum and adenomatous polyps. A review of epidemiologic findings. Cancer 28, 14-24.
- 1973. Cancer of the large intestine: Epidemiologic findings. Dis Colon Rectum 16, 371-377.
- Helwig, E.B. 1947. The evolution of adenomas of the large intestine and their relation to carcinoma. Surg Gynecol Obstet 84, 36-49.
- Horn, R.C., Jr. 1971. Malignant potential of polypoid lesions of the colon and rectum. Cancer 28, 146-152.
- Hultborn, K.A. 1952. Cancer of the colon and rectum. A clinical and pathological study with special reference to the possibilities of improving the diagnostic methods and the therapeutic results in adenocarcinoma. Acta Chir Scand, Suppl. 172.
- 1954. The causal relationship between benign epithelial tumors and adenocarcinoma of the colon and rectum. Acta Radiol (Stockh), Suppl. 113.

- 1968. Potential malignancy of colonic and rectal polyps. Surgical aspects on diagnosis, therapy and cancer prevention. In Thule international symposia. Cancer and aging (Stockholm, 1967), pp. 229-252. Nordiska Bokhandelns Förlag, Stockholm.
- Jackman, R.J. & Beahrs, O.H. 1968. Tumors of the large bowel. In Major problems in clinical surgery, vol. 8. Saunders, Philadelphia, London, Toronto.
- de Jong, U.W., Day, N.E., Muir, C.S., Barclay, T.H.C., Bras, G., Foster, F.H., Jussawalla, D.J., Kurihara, M., Linden, G., Martinez, I., Payne, P.M., Pedersen, E., Ringertz, N. & Shanmugaratnam, T. 1972. The distribution of cancer within the large bowel. Int J Cancer 10, 463-477.
- Kalus, M. 1972. Carcinoma and adenomatous polyps of the colon and rectum in biopsy and organ tissue culture. Cancer 30, 972-982.
- Lane, N., Kaplan, H. & Pascal, R.R. 1971. Minute adenomatous and hyperplastic polyps of the colon: divergent patterns of epithelial growth with specific associated mesenchymal changes. Contrasting roles in the pathogenesis of carcinoma. Gastroenterology 60, 537-551.
- Lane, N. & Lev, R. 1963. Observations on the origin of adenomatous epithelium of the colon. Serial section studies of minute polyps in familial polyposis. Cancer 16, 751-764.
- Langeland, P. 1970. Population screening for female breast tumours. A clinical investigation. Acta Radiol (Stockh), Suppl. 297.
- Lawrence, J.C. 1936. Gastrointestinal polyps. Statistical study of malignancy incidence. Am J Surg 31, 499-505.
- Lescher, T.C., Dockerty, M.B., Jackman, R.J. & Beahrs, O.H. 1967. Histopathology of the larger colonic polyp. Dis Colon Rectum 10, 118-124.
- Morson, B.C. 1962. Some peculiarities in the histology of intestinal polyps. Dis Colon Rectum 5, 337-344.
- Morson, B.C. & Bussey, H.J.R. 1970. Predisposing causes of intestinal cancer. In Current problems in surgery. A series of monthly clinical monographs. February issue. Year Book Medical Publishers, Chicago.
- Morson, B.C. & Dawson, I.M.P. 1972. Gastrointestinal pathology. Blackwell Scientific Publications, Oxford, London, Edinburgh, Melbourne.

- Pagtalunan, R.J.G., Dockerty, M.B., Jackman, R.J. & Anderson, M.J., Jr. 1965. The histopathology of diminutive polyps of the large intestine. Surg Gynecol Obstet 120, 1259-1265.
- Potet, F. & Soullard, J. 1971. Polyps of the rectum and colon. Gut 12, 468-482.
- Rider, J.A., Kirsner, J.B., Moeller, H.C. & Palmer, W. L. 1954. Polyps of the colon and rectum. Their incidence and relationship to carcinoma. Am J Med 16, 555-564.
- 1959. Polyps of the colon and rectum. A four-year to nine-year follow-up study of five hundred thirty-seven patients. JAMA 170, 633-638.
- Sanfelippo, M.P.M. & Beahrs, O.H. 1972. Factors in the prognosis of adenocarcinoma of the colon and rectum. Arch Surg 104, 401-406.
- Schmieden, V. & Westhues, H. 1927. Zur Klinik und Pathologie der Dickdarmpolypen und deren klinischen und pathologisch-anatomischen Beziehungen zum Dickdarmkarzinom. Dtsch Z Chir 202, 1-124.
- Spjut, H.J. & Spratt, J.S., Jr. 1965. Endemic and morphologic similarities existing between spontaneous colonic neoplasms in man and 3:2'-dimethyl-4-aminobiphenyl induced colonic neoplasms in rats. Ann Surg 161, 309-324.
- Spratt, J.S., Jr. & Ackerman, L.V. 1960. Relationship of the size of colonic tumours to their cellular composition and biological behavior. Surg Forum 10, 56-61.
- Spratt, J.S., Jr., Ackerman, L.V. & Moyer, C.A. 1958. Relationship of polyps of the colon to colonic cancer. Ann Surg 148, 682-696.
- Spratt, J.S., Jr. & Watson, F.R. 1971. The rationale of practice for polypoid lesions of the colon. Cancer 28, 153-159.
- Thomas, J.F., Dockerty, M.B. & Waugh, J.M. 1948. Multiple primary carcinomas of the large intestine. Cancer 1, 564-573.
- Turell, R. & Haller, J.D. 1964. A re-evaluation of the malignant potential of colorectal adenomas. Surg Gynecol Obstet 119, 867-887.
- Weakley, F.L. & Swinton, N.W. 1962. Follow-up study of patients with benign mucosal polyps of the rectum. Dis Colon Rectum 5, 345-348.
- Welch, C.E. 1964. Polypoid lesions of the gastrointestinal tract. In Major problems in clinical surgery, vol. 2. Saunders, Philadelphia and London.
- Welin, S. 1967. Results of the Malmö technique of colon examination. JAMA 199, 369-371.

- 1968. Polyps in colon-rectum and cancer. Radiological diagnosis. In Thule international symposia. Cancer and aging (Stockholm, 1967), pp. 253-257. Nordiska Bokhandelns Förlag, Stockholm.
- Wenckert, A. 1963. Cancer of the colon and rectum. Acta Chir Scand, Suppl. 332, 73-79.
- Winblad, S. & Friberg, S. 1956. Observations on the pathology of polyps of the colon. Acta Pathol Microbiol Scand, Suppl. 111, 89-91.
- Wychulis, A.R., Dockerty, M.B., Jackman, R.J. & Beahrs, O.H. 1967. Histopathology of small polyps of the large intestine. Surg Gynecol Obstet 124, 87-92.

APPENDIX

ADDITIONAL TABLES

Table V Sub-site distribution of carcinomas in necropsy series (I). Two solitary carcinomas with unknown site and three cases with carcinoma on the basis of ulcerative colitis are not included.

<u>Site</u>	<u>Solitary</u>		<u>Multiple</u>		<u>Total</u>	
	<u>No.</u>	<u>%</u>	<u>No.</u>	<u>%</u>	<u>No.</u>	<u>%</u>
Caecum-asc. colon	37	23.0	6	20.7	43	22.6
Transv. colon incl. flexures	19	11.8	4	13.8	23	12.1
Desc. colon	4	2.5	1	3.4	5	2.6
Sigmoid colon	63	39.1 \	13	44.8 \	76	40.0 \
		62.7		62.0		62.6
Rectum	<u>38</u>	23.6 /	<u>5</u>	17.2 /	<u>43</u>	22.6 /
All sites	161		29		190	

Table VI Sub-site distribution of carcinomas in clinical series (II).

<u>Site</u>	<u>Solitary</u>		<u>Multiple</u>		<u>Total</u>	
	No.	%	No.	%	No.	%
Caecum-asc. colon	152	16.6	22	23.2	174	17.2
Transv. colon incl. flexures	101	11.1	13	13.7	114	11.3
Desc. colon	37	4.0	8	8.4	45	4.5
Sigmoid colon	273	29.9 \ 68.3	22	23.2 \ 54.7	295	29.2 \ 67.0
Rectum	<u>351</u>	38.4 /	<u>30</u>	31.6 /	<u>381</u>	37.8 /
All sites	914		95		1009	

Table VII Sub-site distribution of solitary polyps in clinical series (II, IV).

Solitary BEN in this table is to be understood as

- a BEN which is the only polyp found in the patient, or
- a BEN which is associated with meta-plastic or non-epithelial polyps, but no other BEN, provided all polyps in the case were examined histologically.

<u>Site</u>	<u>Solitary polyps</u>		<u>Solitary BEN</u>	
	No.	%	No.	%
Caecum-asc.colon	13	12.0	10	11.0
Transv.colon incl.flexures	15	13.9	8	8.8
Desc.colon	9	8.3	4	4.4
Sigmoid colon	33	30.5 \ 65.7	32	35.2 \ 75.8
Rectum	<u>38</u>	35.2 /	<u>37</u>	40.7 /
All sites	108		91	

STATISTICAL ANALYSES*

A. The following calculations were performed with the χ^2 -test. In 2x2 tables Yate's correction was used.

1. Results in Chapter IV.

Results in Table I:

	Cases with polyps	Cases with- out polyps
Unselected necropsy series (I)	380	2661
Cases with carcinoma in necropsy series (I)	47	133
	0.001 > p	

	Cases with polyps	Cases with- out polyps
Unselected necropsy series (I)	380	2661
Clinical series of carcinomas (II)	213	747
	0.001 > p	

	Cases with polyps	Cases with- out polyps
Clinical series of carcinomas (II)	213	747
Clinical series of multiple carcinomas (III)	28	16
	0.001 > p	

Results in Table II:

	Multiple polyps	Solitary polyps
Unselected necropsy series (I)	173	207
Cases with carcinoma in necropsy series (I)	28	19
	p > 0.05	

*Statistical adviser: Bo Nilsson, M.D.

	Multiple polyps	Solitary polyps
Unselected necropsy series (I)	173	207
Clinical series of carcinomas (II)	103	110
	$p > 0.05$	

	Multiple polyps	Solitary polyps
Unselected necropsy series (I)	173	207
Clinical series of multiple carcinomas (III)	21	7
	$0.01 > p > 0.001$	

(Results in Fig 5 - see under B).

Results in Fig 6:

	Caecum and ascend. colon	Rest of colon- rectum
All carcinomas in necropsy series (I)	43	147
All polyps in necropsy series (I)	112	354
	$p > 0.05$	
	Rectum and sigmoid. colon	Rest of colon
All carcinomas in necropsy series (I)	119	71
All polyps in necropsy series (I)	212	254
	$0.001 > p$	

	Caecum and ascend. colon	Rest of colon- rectum
Solitary carcinomas in necropsy series (I)	37	124
Solitary polyps in necropsy series (I)	39	164
	p > 0.05	

	Rectum and sigmoid colon	Rest of colon
Solitary carcinomas in necropsy series (I)	101	60
Solitary polyps in necropsy series (I)	116	87
	p > 0.05	

Results in Fig 7:

	Caecum and ascend. colon	Rest of colon- rectum
All carcinomas in clinical series (II)	174	835
All polyps in clinical series (II)	109	312
	0.001 > p	

	Rectum and sigmoid colon	Rest of colon
All carcinomas in clinical series (II)	676	333
All polyps in clinical series (II)	219	202
	0.001 > p	

	Caecum and ascend. colon	Rest of colon- rectum
Solitary carcinomas in clinical series (II)	152	762
Solitary polyps in clinical series (II)	13	95
	$p > 0.05$	

	Rectum and sigmoid colon	Rest of colon
Solitary carcinomas in clinical series (II)	624	290
Solitary polyps in clinical series (II)	71	37
	$p > 0.05$	

Results in Table III:

	Malignant polypoid tumours	Benign polyps
5 - 10 mm	13	64
> 10 mm	79	55
	$0.001 > p$	

2. Results in Chapter V.

Analysis of relative difference between patients with carcinoma and BEN, versus patients with polyps in necropsy series:

	Cases with polyps	Cases with- out polyps
Clinical series of carcinomas (only BEN regarded as polyps) (IV)	174	786
Unselected necropsy series (I)	380	2661
	$0.001 > p$	

Results in Fig 15:

	Caecum and ascend. colon	Rest of colon- rectum
All carcinomas in clinical series (II)	174	835
All BEN in clinical series (IV)	95	213
	0.001 > p	
	Rectum and sigmoid colon	Rest of colon
All carcinomas in clinical series (II)	676	333
All BEN in clinical series (IV)	149	159
	0.001 > p	
	Caecum and ascend. colon	Rest of colon- rectum
Solitary carcinomas in clinical series (II)	152	762
Solitary BEN in clinical series (IV)	10	81
	p > 0.05	
	Rectum and sigmoid colon	Rest of colon
Solitary carcinomas in clinical series (II)	624	290
Solitary BEN in clinical series (IV)	69	22
	p > 0.05	

Results in Fig 17:

Size	Adenomatous polyps	Villous lesions
< 5 mm	159	22
5 - 10 mm	42	21
> 10 mm	25	24
	0.001 > p	

Results in Fig 18:

	Moderate or higher	Lower than moderate
Adenomatous polyps	101	137
Adenovillous lesions	16	54
	0.01 > p > 0.001	

Analysis of sex difference in differentiation of BEN:

	Moderate or higher	Lower than moderate
BEN in men	68	125
BEN in women	49	66
	p > 0.05	

Results in Fig 19:

	Moderate or higher	Lower than moderate
BEN in right colon	58	69
BEN in left colon	38	72
BEN in rectum	22	49
	0.001 > p	

Results in Fig 20:

Size:	Moderate or higher	Lower than moderate
< 5 mm	81	101
5 - 10 mm	19	44
> 10 mm	13	36
	0.001 > p	

Analysis of differences in differentiation of BEN according to localisation of coexisting carcinoma:

	Advanced dysplasia or low grade of diff.	Higher grades of diff.
BEN in same segment as carcinoma	17	29
BEN in segment adjacent to that of carcinoma	5	12
BEN in segment not adjacent to that of carcinoma	8	23
	0.05 > p > 0.02	

3. Analysis of results in Chapter VI.

Analysis of difference between number of patients with new polyps in the polyp series and in the control series.

	Cases with new polyps	Cases without new polyps
Polyp series	24	91
Control series	8	107
	0.01 > p > 0.001	

4. Analyses of results discussed in Chapter VII.

Comparison of the necropsy series (I) and the clinical series (II) regarding relative frequency of polyps and carcinomas in the rectum and sigmoid colon taken together:

	Rectum and sigmoid colon	Rest of colon
All carcinomas in necropsy series (I)	119	71
All carcinomas in clinical series (II)	676	333
	$p > 0.05$	
	Rectum and sigmoid colon	Rest of colon
All polyps in necropsy series (I)	212	254
All polyps in clinical series (II)	219	202
	$p > 0.05$	
	Rectum and sigmoid colon	Rest of colon
Solitary carcinomas in necropsy series (I)	101	60
Solitary carcinomas in clinical series (II)	624	290
	$p > 0.05$	
	Rectum and sigmoid colon	Rest of colon
Solitary polyps in necropsy series (I)	116	87
Solitary polyps in clinical series (II)	71	37
	$p > 0.05$	

Analysis of sex differences in frequencies of BEN and carcinoma, respectively, in the rectum:

	Rectum	Colon
BEN in men (IV)	56	137
BEN in women (IV)	15	100

$0.01 > p > 0.001$

	Rectum	Colon
Carcinomas in men (II)	217	312
Carcinomas in women (II)	164	316

$0.05 > p > 0.01$

	Rectum and sigmoid colon	Rest of colon
BEN in men (IV)	105	88
BEN in women (IV)	44	71

$0.01 > p > 0.001$

B. In the statistical analysis of sex-ratios the difference between the observed number (O) and the expected number (E) was compared with the standard deviation of the observed number which equals $\sqrt{E}$. The difference was regarded as significant ($p < 0.05$) when it exceeded $2 \cdot \sqrt{E}$. The results are tabulated below. The first 10 lines correspond to Fig V (Chapter IV) and the last line to results given in Chapter V.

<u>Combination</u>	<u>Men</u>	<u>Women</u>	<u>Significance</u>
Carcinoma (I)	85	95	-
Carcinoma (II)	497	463	-
Polyps (I)	240	140	+
Carcinoma and polyps (I)	30	17	-
Carcinoma and polyps (II)	130	83	+
Multiple polyps (I)	117	56	+
Carcinoma and multiple polyps (I)	19	8	-
Multiple carcinomas (III)	28	16	-
Multiple carcinomas and polyps (III)	19	9	-
Multiple carcinomas and multiple polyps (III)	14	7	-
Carcinoma and BEN (IV)	107	67	+

